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(54) Title: PACK FOR USE IN, AND METHOD OF HORMONAL REPLACEMENT THERAPY

(57) Abstract

Pack comprising a first delivery system containing estrogen for subdermal application, and a second delivery system containing progestin for administration into the uterine cavity, for joint administration of both delivery systems in hormonal replacement therapy of a postmenopausal female. The invention also concerns a method of hormonal replacement therapy comprising administering subdermally an effective amount of estrogen and an effective amount of progestin into the uterine cavity.

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Pack for use in, and method of hormonal replacement therapy

FIELD OF INVENTION

The present invention relates to a pack for use in, and a method of treatment of climacteric women, especially for the treatment of post-menopausal symptoms. In particular the present invention relates to a combination treatment method and a pack for use therein, wherein, in the broadest sense of the invention, estrogen is administered subdermally and progestin is administered into the uterine cavity.

BACKGROUND OF THE INVENTION

The benefits of estrogen therapy in climacteric women are well established. It is an effective treatment for menopausal symptoms, a preventative measure for osteoporosis, and it also appears to be associated with a reduction of risk of cardiovascular disease.

Nevertheless, it is also well established that by inducing endometrial proliferation, the estrogen-only therapy increases the risk of endometrial hyperplasia and carcinoma. Accordingly, unopposed estrogen is not recommended for women who have an intact uterus. In order to avoid the risk of endometrial hyperplasia and carcinoma, supplementary oral progestin has been administered concomitantly with the estrogen to produce endometrial shedding. The progestin is most commonly administered cyclically for 10 or 12 days of each treatment cycle. However, conventional progestin administration appears to have some drawbacks:

- Many oral progestins undergo first-pass liver metabolism, which may possibly add to the occurrence of

longterm risks, especially through their effects on lipid metabolism.

- Cyclic treatment produces monthly withdrawal bleedings, which some women find unacceptable, and has been found to be a major reason for discontinuation of hormone replacement therapy.

- Women often experience unwanted side-effects while taking the oral progestin (pseudo pre-menstrual syndrome).

Levonorgestrel is used for hormonal replacement therapy in oral tablets formulations in daily doses of 75 to 250 µg. A hormone releasing intrauterine contraceptive device, which releases the progestogen levonorgestrel (LNG) at a low rate of 20 µg/24 h, has already been widely tested as a contraceptive (c.f. e.g. US patent 4,341,728). Large scale studies have shown that, in the presence of the device, the endometrium remains in a nonproliferative, atrophic state (Silverberg et al., Int. J. Gynecol. Pathol. 1986;5:235-41).

Oral estrogen undergoes extensive first-pass metabolism, and the doses needed for systemic effect are high (1 to 2 mg daily of estradiol valerate, or 0.625 mg of conjugated estrogens). The first-pass metabolism can be overcome by transdermal administration as transdermal patches of 25 to 100 µg/24h, or percutaneous gels. The limitation with these methods is local irritation and the need to administer the treatment every day or twice a week. Estrogen-cholesterol pellets have been found to increase circulating estrogen levels, but their effect declines in a couple of months' time, and may be unpredictable (Garnett et al., Brit. J. Obstet. Gynecol. 1990; 97:917-921).

Recently a combination hormone replacement therapy was published (Andersson, K. et al., Obstetrics & Gynecology, vol. 79, no. 6, June 1992) including the oral administration of estrogen in combination with levonorgestrel either orally, or locally in the form of an IUD. This combination therapy is, however, still associated with the negative effects arising from administering estrogen orally.

DETAILED DESCRIPTION OF THE INVENTION

The subject of the present invention is a combination therapy or treatment, as well as a pack for use therein, intended for postmenopausal or climacteric women comprising the simultaneous subdermal administration of estrogen and the administration of progestin locally via the uterus.

Thus the invention, in a first aspect, concerns a pack comprising a first delivery system containing estrogen for subdermal application, and a second delivery system containing progestin for administration into the uterine cavity, for joint administration of both delivery systems in hormonal replacement therapy of a postmenopausal female.

According to a second embodiment, the invention concerns the use of estrogen and progestin presented separately but for joint administration in a pack comprising a first estrogen containing delivery system for subdermal application, and a second progestin containing delivery system for administration into the uterine cavity, for joint administration of both delivery systems in hormonal replacement therapy of a postmenopausal female.

The invention also concerns a method of hormonal replacement therapy of postmenopausal women, comprising

administering an effective amount of estrogen subdermally and an effective amount of progestin into the uterine cavity.

For the administration of progestin, preferably a intrauterine device of the kind disclosed in the US-patent 4,341,728 is used, which patent is included herein for reference. The device has a T-shaped frame, the hormone being homogenously dispersed in a silicone rubber, optionally covered by a membrane and mounted on the vertical arm of the T. Naturally any other type of intrauterine device capable of releasing progestin at the desired rate is applicable. The progestin is preferably levonorgestrel, which according to a suitable embodiment of the invention is incorporated in an amount sufficient to be released at a rate of 7-30 µg/daily.

The parenteral administration of estrogen is preferably in the form of an estrogen subdermal implant, for example of the NORPLANT type. A suitable implant is in the form of a piece of silicone tubing carrying an estradiol containing matrix of e.g. a silicone polymer, such as polydimethylsiloxane, releasing the drug over an extended period of time at a predetermined rate. The drug is incorporated in an amount sufficient to be released at a rate of 20-60 µg/daily.

Hormonal replacement therapy is usually intended for long periods of time (months to years), but preferably the combination treatment should be extended for at least one year.

The concurrent use of a levonorgestrel-releasing IUD with estrogen treatment has several advantages over orally administered progestins and thus may lead to more acceptable and safer forms of combined hormonal replacement therapy. For both the progestin and the

estrogen, the doses required daily (released from the delivery systems) are very low compared with the doses needed orally. The subject is protected for more than a year from estrogen deficiency and endometrial proliferation by a single administration of the two delivery systems. No daily or weekly motivation to remember to take tablets or change patches is needed. The women do not need to menstruate regularly in the age when bleeding is considered a nuisance.

The following tests were carried out.

Example 1

Thirty-six postmenopausal women seeking treatment for their climacteric symptoms were recruited for the study. They all were fitted with an intrauterine device of a type corresponding to that of the US-patent 4,341,728 releasing 20 µg/24h levonorgestrel. An implant (of the NORPLANT type) releasing 20 µg/24h of estradiol was placed subdermally to 16 of these women, and three of the same implants were placed subdermally to 20 women.

Serum estradiol concentrations were measured at baseline and after 2, 6 and 12 months of therapy. The following mean concentrations (pmol/1) were found, and they showed that the implants increased the womens' serum estrogen levels in a dose-dependent manner:

Time	Implant group	
	1 implants	3 implants
Baseline	90	110
2 mo.	150	205
6 mo.	130	170
12 mo.	130	170

Serum levonorgestrel concentrations were measured at the same intervals, and the median levels (pg/ml) were:

Time	Implant group	
	1 implants	3 implants
Baseline	-	-
2 mo.	267	321
6 mo.	208	287
12 mo.	257	269

Climacteric symptoms were assessed on a visual analogue scale with a score of 0 for no symptoms and a maximum score of 100. For hot flushes, the following median scores were observed, showing improvement of climacteric symptoms:

Time	Implant group	
	1 implants	3 implants
Baseline	42	51
2 mo.	2	3
6 mo.	8	4
12 mo.	11	3

During the same period, the menstrual bleedings were recorded. The following percentage of women had no bleeding within 30-day "cycles" indicating progressive suppression of uterine lining caused by the levo-norgestrel-releasing intrauterine device:

Time	Per cent of women
2 mo.	6
6 mo.	50
12 mo.	72

Claims

1. Pack comprising a first delivery system containing estrogen for subdermal application, and a second delivery system containing progestin for administration into the uterine cavity, for joint administration of both delivery systems in hormonal replacement therapy of a postmenopausal female.

2. The pack according to claim 1, wherein the first delivery system is a subdermal implant.

3. The pack according to claim 2, wherein the estrogen is estradiol.

4. The pack according to the claim 3, wherein estrogen is present in the first delivery system in an amount sufficient to provide for a release of 20-60 µg daily.

5. The pack according to claim 1, wherein the second delivery system is a progestin-releasing intrauterine device (IUD).

6. The pack according to claim 5, wherein the progestin is levonorgestrel.

7. The pack according to the claim 6, wherein levonorgestrel is present in the second delivery system in an amount sufficient to provide for a release of 7-30 µg daily.

8. Use of estrogen and of progestin presented separately but for joint administration in a pack according to any one of the preceding claims, for hormonal replacement therapy of a postmenopausal female.

9. Method of hormonal replacement therapy of postmeno-

pausal women, comprising administering an effective amount of estrogen subdermally and an effective amount of progestin into the uterine cavity.

10. Method according to claim 9 comprising administering estrogen in the form of a subdermal implant.

11. Method according to claim 10, wherein 20-60 µg of estradiol is administered daily.

12. Method according to claim 9, comprising administering levonorgestrel into the uterine cavity.

13. Method according to claim 12, wherein levonorgestrel is administered in an amount of 7-30 µg daily.

14. Method according to claim 9, wherein estrogen is administered in the form of a subdermal implant, and levonorgestrel is administered into the uterine cavity.

15. Method according to claim 14, wherein estrogen is administered in an amount of 20-60 µg and levonorgestrel in an amount of 7-30 µg daily for a period exceeding one year.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 94/00292

A. CLASSIFICATION OF SUBJECT MATTER

IPC : A61K 9/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC : A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, EMBASE, WPI, WPIL, CLAIMS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Dialog Information Services, file 155, MEDLINE, Dialog accession no. 08741595, Medline accession no. 94056595, Suhonen SP: "Sustained-release subdermal estradiol implants: a new alternative in estrogen replacement therapy", & Am J Obstet Gynecol (UNITED STATES) Nov 1993, 169 (5) p1248-54 --	1-8
Y	OBSTETRICS AND GYNECOLOGY, Volume 79, No 6, June 1992, Kerstin Andersson, MD et al, "Intrauterine Release of Levonorgestrel - A New Way of Adding Progestogen in Hormone Replacement Therapy" page 963 - page 967 --	1-8

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Dialog Information Services, file 155, MEDLINE, Dialog accession no. 082927965, Medline accession no. 93002796, Owen EJ et al: "25 mg oestradiol implants--the dosage of first choice for sub-cutaneous oestrogen replacement therap", & Br J Obstet Gynaecol (ENGLAND) Aug 1992, 99 (8) p671-5 --	1-8
A	Dialog Information Services, file 155, MEDLINE, Dialog accession no. 07672966/5, Medline accession no. 91191966, Balfour JA et al: "Transdermal estradiol. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of menopausal complaints", & Drugs (UNITED STATES) Oct 1990, 40 (4) p561-82 -- --------	1-8